

REMARKS

The Official Action dated September 10, 2004 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present amendment, claims 1, 3-6, 8-15 and 18-20 have been amended for various matters of form in accordance with customary U.S. patent practice. Claim 1 has also been amended to recite that the maximum duration of each cycle is four minutes, as set forth in the specification, for example, at page 3, lines 23-25. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

Claims 1, 4, 5, 8, 9, 12, 13 and 18-20 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner objected to use of the terms "short" in claim 1, "phase of the cycle" in claims 4, 10 and 11, "only during certain segments of the process" in claims 5, 12 and 13, "depending on the promoter used" in claims 8 and 18-20, and "recombinant product" in claim 9. This rejection is traversed and reconsideration is respectfully requested. That is, the term "short" has been omitted from claim 1 and the remaining phrases objected to by the Examiner have been clarified. It is therefore submitted that claims 1-20 are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph, whereby the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1, 2, 5-8, 14, 16, 18 and 20 were rejected under 35 U.S.C. §102(b) as being anticipated by Kerns et al, *Acta Biotechnol*, 8(3): 285-289 (1988). The Examiner asserted

that Kerns et al describe a fermentation process that increases the yield of recombinant protein where the carbon/energy source is increased by oscillation.

Applicants submit however that the methods defined by claims 1, 2, 5-8, 14, 16, 18 and 20 are not anticipated by and are patentably distinguishable from the teachings of Kerns et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, as defined by claim 1, the present invention is directed to a method for increasing the yield of recombinant protein in a microbial fermentation process. Specifically, the concentration of a carbon/energy source in the culture of a microbial fermentation process for producing recombinant protein is oscillatingly reduced or increased in cycles. The maximum duration of each cycle is four minutes. As set forth in the present specification, for example at page 3, lines 23-26, the present methods surprisingly have a positive influence on product yield.

The English summary of the Kerns et al publication indicates that the publication discloses cellulase formation employing an oscillating-fed-batch-technique (OFB) with feed-back-controlled intermittent addition of the substrate. However, there is no teaching in the English summary of a method as recited in claim 1, wherein the concentration of a carbon/energy source in the culture of a microbial fermentation process for producing recombinant protein is oscillatingly reduced or increased in cycles with the maximum duration of each cycle being four minutes.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999). In view of the failure of the Examiner to demonstrate that Kerns et al disclose each and every element of claim 1, Kerns et

al do not anticipate claim 1, or claims 2, 5-8, 14, 16, 18 or 20 dependent thereon. It is therefore submitted that the rejection under 35 U.S.C. §102 based on Kerns et al has been overcome. Reconsideration is respectfully requested.

Claim 1 was rejected under 35 U.S.C. §102(b) as being anticipated by the Suzuki et al Japanese reference JP 56-26592. The Examiner asserted that Suzuki et al describe a fermentation process to denitrify waste water where the carbon/energy source is increased by oscillation. The Examiner asserted that the claimed preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure.

However, Applicants submit that the method defined by claim 1 is not anticipated by and is patentably distinguishable from Suzuki et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

As noted above, claim 1 is directed to a method for increasing the yield of recombinant protein in a microbial fermentation process. Specifically, claim 1 requires oscillatingly reducing or increasing in cycles the concentration of a carbon/energy source in the culture of a microbial fermentation process for producing recombinant protein. On the other hand, as noted by the Examiner, Suzuki et al are directed to a biological denitrification method for waste water wherein nitrogen oxide is removed from the waste water using denitrifying bacteria adhered on a medium. Applicants find no teaching by Suzuki et al relating to a method for increasing the yield of recombinant protein in a microbial fermentation process, or for oscillatingly reducing or increasing the concentration of a carbon/energy source in the culture of such a process for producing recombinant protein as required by claim 1. In view of these deficiencies in the teachings of Suzuki et al, Suzuki et

al do not describe each and every element of claim 1, and therefore do not anticipate claim 1, or any of the claims dependent thereon, *In re Robertson, supra*. It is therefore submitted that the rejection under 35 U.S.C. §102 based on Suzuki et al has been overcome. Reconsideration is respectfully requested.

Claims 1-7 and 10-17 were rejected under 35 U.S.C. §102(e) as being anticipated by the Castan U.S. Patent No. 6,680,181. The Examiner asserted that Castan teaches a method for the production of recombinant peptide by fed batch cultivation of a microorganism in a bioreactor, wherein the cultivation is carried out by the addition of organic carbon source and oscillation feed.

This rejection is traversed on the basis that Castan is not proper prior art with respect to the present application. That is, Castan has a U.S. filing date of December 8, 2000 and claims priority to U.S. provisional application Serial No. 60/172,822 filed December 21, 1999. On the other hand, the present application is a 371 of PCT/EP00/0894 filed September 13, 2000, which claims priority to German Application DE199 43 919 filed September 14, 1999. A verified English language translation of the German priority application is currently being prepared and will be submitted as soon as it is received by the undersigned. The verified English language translation will demonstrate that the present application is entitled to an effective filing date of September 14, 1999, and thus prior to the earliest U.S. filing date of Castan, whereby Castan is not prior art with respect to the present application. It is therefore submitted that the rejection based on Castan should be withdrawn. Reconsideration is respectfully requested.

Finally, claims 1-7 and 10-17 were rejected under 35 U.S.C. §102(a) as anticipated by the Nakamura et al U.S. Patent No. 5,912,113. The Examiner asserted that Nakamura et al

disclose a method of culturing microorganisms in a batch culture wherein glucose is added to the culture media in an oscillating manner and the time between which glucose is added to the culture media can be less than two minutes as well as less than or equal to 30 minutes, thus changing the dosage rate.

However, as set forth below, Applicants submit that the methods defined by claims 1-7 and 10-17 are not anticipated by and are patentably distinguishable from Nakamura et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The method for increasing the yield of recombinant protein in a microbial fermentation process as defined by claim 1 is discussed in detail above. As the maximum duration of each cycle is four minutes, one of ordinary skill in the art will appreciate that the concentration of the carbon/energy source in the culture is varied over short periods of time. Applicants submit that Nakamura et al provide no teaching or suggestion in this regard. First, Applicants find no disclosure either in the abstract or column 10 of Nakamura et al indicating that the time between which glucose is added to the culture media is less than two minutes or less than or equal to 30 minutes, as asserted by the Examiner. Particularly, τ which is discussed in the Abstract of Nakamura et al and at column 10 is the time period when the addition of feed solution was terminated to determine the feeding rate.


Contrary to the present methods wherein the concentration of a carbon/energy source in the culture is oscillatingly reduced or increased in cycles having a maximum duration of four minutes, the objective of Nakamura et al is to maintain the carbon source concentration in the culture medium "at a constant low level" (abstract, line 5). For example, the Examiner's attention is directed to Fig. 5 which demonstrates Nakamura et al's objective of maintaining a sugar concentration at a relatively constant level over an 80 hour reaction

period. As further shown in Fig. 5 and described at columns 9 and 10, Nakamura et al teach that each time period for adding the feed solution was set at three hours (column 9, lines 48 and 61; column 10, lines 21-22). Applicants find no teaching by Nakamura et al relating to oscillatingly reducing or increasing concentration of a carbon source in cycles having a maximum duration of four minutes as presently claimed. Thus, Nakamura et al do not describe each and every element of claim 1 and therefore do not anticipate claim 1, or claims 2-7 and 10-17, under 35 U.S.C. §102, *In re Robertson, supra*. It is therefore submitted that the rejection under 35 U.S.C. §102 based on Nakamura et al has been overcome.

Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§102 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

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